EXHIBIT J

9/9/91

PATENT
11509-A-1-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Michael C. Pirrung et al.
Serial No. 492,462
Filed: March 7, 1990
For: VERY LARGE SCALE IMMOBILIZED POLYMER SYNTHESIS

Examiner: J. Stall
Art Unit: 180

AMENDMENT

San Francisco, CA 94105

COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Sir:

In response to the Office Action mailed March 20, 1991 (Paper No. 21), the period for response being extended as a result of the enclosed Petition for Extension of Time and requisite fee, please amend the above-identified application as follows:

IN THE CLAIMS:

Please cancel Claims 1, 26, and 55-105 without prejudice to renewal in a continuation, divisional or other related application.

Please amend Claims 2-11, 13, 16-21, 27, 36, 40, 44, and 47 as follows:

2. (Amended) The method as recited in claim [1] 6 wherein said steps of exposing to an activator use an activator selected from the group consisting of ion beams, electron beams, gamma rays, x-rays, ultra-violet radiation, light, infra-red radiation, microwaves, electric currents, radiowaves, and combinations thereof.

3. (Amended) The method as recited in claim [1] 6 wherein said protective groups are photosensitive protective groups.

4. (Amended) The method as recited in claim [1] 6 wherein said steps of exposing to an activator are steps of applying light to selected regions of said substrate.

5. (Amended) The method as recited in claim [1] 6 wherein said first and the second monomers are amino acids.

6. (Amended) [The method as recited in claim 1 further comprising a step of]. A method of preparing and screening sequences comprising:

a) exposing a first selected region of a substrate to an activator to remove a protective group;

b) exposing at least said first region to a first monomer having a protective group;

c) exposing a second selected region to an activator to remove a protective group, said second region at least partially overlapping said first region;

d) exposing at least said second region to a second monomer so as to synthesize at least first and second sequences on said substrate; and

f) screening said sequences on said substrate for affinity with a receptor, said step of screening [further] comprising [the] steps of exposing said substrate to said receptor and testing for the presence of said receptor in said first and said second region.

7. (Amended) The method as recited in [claim 6] claims 5 or 6 wherein said receptor is an antibody.

8. (Amended) The method as recited in claim [1] 6 wherein said substrate is selected from the group consisting of polymerized Langmuir Blodgett film, functionalized glass, germanium, silicon, polymers, (poly)tetrafluoroethylene, polystyrene, gallium arsenide, and combinations thereof.

9. (Amended) The method as recited in claim [1] 6 wherein said protective group is selected from the group consisting of ortho-nitrobenzyl derivatives, 6-nitroveratryloxy-carbonyl, 2-nitrobenzyloxycarbonyl, cinnamoyl derivatives, and mixtures thereof.

10. (Amended) The method as recited in claim [1] 6 wherein said first and second regions each have total areas of less than 1 cm^2.

11. (Amended) The method as recited in claim [1] 6 wherein said first and second regions each have total areas of between about 1 μm^2 and 10,000 μm^2.

13. (Amended) The method as recited in claim [1] 6 wherein said steps of exposing to an activator are carried out with a solution in contact with said substrate.

16. (Amended) The method as recited in claim [1] 6 wherein the steps of exposing to an activator further comprise steps of:

a) placing a mask adjacent to said substrate, said mask having substantially transparent regions and substantially opaque regions at a wavelength of light; and

b) illuminating said mask with a light source, said light source producing at least said wavelength of light.

17. (Amended) The method as recited in claim [1] 6 wherein said steps are repeated so as to synthesize 10^3 or more different sequences on said substrate.

18. (Amended) The method as recited in claim [1] 6 wherein said steps are repeated so as to synthesize 10^6 or more different sequences on said substrate.

19. (Amended) A method of synthesizing a plurality of chemical sequences[, said chemical sequences comprising at least a first and a second monomer,] comprising the steps of:

a) at a first region on a substrate having at least a first and a second region, said first and said second region each comprising a substrate protective group, activating said first region to remove said substrate protective group in said first region;

b) exposing said first monomer to said substrate, said first monomer further comprising a first monomer protective group, said first monomer binding at said first region;

c) activating said second region to remove said substrate protective group in said second region;

d) exposing said second monomer to said substrate, said second monomer further comprising a second monomer

protective group, said second monomer binding at said second region;

e) activating said first region to remove said first monomer protective group;

f) exposing a third monomer to said substrate, said third monomer binding at said first region to produce a first sequence;

g) activating said second region to remove said second monomer protective group;[and]

h) exposing a fourth monomer to said substrate, said fourth monomer binding at said second region to produce a second sequence, said second sequence different from said first sequence; and

i) screening said first and said second sequences for affinity with a first receptor, said step of screening comprising steps of exposing said substrate to said first receptor and testing for the presence of said first receptor.

20. (Amended) A method of synthesizing a plurality of chemical sequences[, said chemical sequences comprising at least a first and a second monomer,] comprising the steps of:

a) on a substrate having at least a first and a second region, deactivating said first region to provide a first protective group in said first region;

b) exposing [said] a first monomer to said substrate, said first monomer binding at said second region;

c) removing said protective group in said first region;

d) deactivating said second region to provide a second protective group in said second region;

e) exposing [said] a second monomer to said substrate, said second monomer binding at said first region;

f) removing said protective group in said second region;

g) deactivating said first region to provide a protective group in said first region;

h) exposing a third monomer to said substrate, said third monomer binding at said second region to produce a first sequence;

i) removing said protective group in said first region;[and]

j) exposing a fourth monomer to said substrate, said fourth monomer binding at said first region to produce a second sequence, said second sequence different than said first sequence; and

k) screening said first and said second sequences for affinity with a first receptor, said step of screening comprising steps of exposing said substrate to said first receptor and testing for the presence of said first receptor.

21. (Twice Amended) A method of synthesizing at least a first polymer sequence and a second polymer sequence on a substrate, said first polymer sequence having a different monomer sequence from said second polymer sequence, comprising the steps of:

a) inserting a first mask between said substrate and an energy source, said mask having first regions and second regions, said first regions permitting passage of energy from said source, said second regions blocking energy from said source;

b) directing energy from said source at said substrate, said energy removing a protective group from first portions of said first polymer under said first regions of said first mask;

c) exposing a second portion of said first polymer to said substrate to create a first polymer sequence;

d) inserting a second mask between said substrate and said energy source, said second mask having first regions and second regions;

e) directing energy from said source at said substrate, said energy removing said protective group under said first regions of said second mask ~~from first~~ portions of said second polymer; [and]

f) exposing a second portion of said second polymer to said substrate, said second portion of said second polymer binding with said first portion of said second polymer to create a second polymer sequence; and

g) screening said first and said second sequences for affinity with a first receptor, said step of screening comprising steps of exposing said substrate to said first receptor and testing for binding of said first receptor.

27. (Amended) The method as recited in [claim 26] claims 19, 20 or 21 wherein said [step of screening is a step of screening with antibodies] receptor is an antibody.

36. (Amended) The method as recited in [claim 26] claims 19, 20 or 21 wherein said receptor further comprises a marker selected from the group consisting of radioactive markers and fluorescent markers and wherein said step of testing for the presence of the receptor [is a step of] detect[ing] said marker.

40. (Amended) The method as recited in [claim 26] claims 19, 20 or 21 further comprising the step of exposing said substrate to a second, labeled receptor, said second, labeled receptor binding at multiple sites on said first receptor.

44. (Amended) A method of screening a plurality of amino acid sequences for binding with a receptor comprising the steps of:

a) on a glass plate having at least a first surface, said at least a first surface comprising a photoprotective material [selected from the group consisting of nitroveratryloxy carbonyl and nitrobenzyloxy carbonyl,] reacting said at least a first surface with a material comprising t-butoxycarbonyl (TBOC) for storage, said glass plate substantially transparent to at least ultraviolet light;

b) exposing said at least a first surface to [TFA] a TBOC removal agent to remove said material comprising t-butoxycarbonyl and [c)] placing said glass plate on a reactor, said reactor comprising a reactor space, said at least a first surface exposed to said reactor space;

[d] c) placing a mask at a first position [on] in proximity with said glass plate, said mask comprising first locations and second locations, said first locations substantially transparent to at least ultraviolet light and said second locations substantially opaque to at least ultraviolet light, said second locations comprising a light blocking material on a first surface of said mask, said first surface of said mask placed in contact with said glass plate;

[e] d) filling said reactor space with a reaction solution;

[f] e) illuminating said mask with at least ultraviolet light, said ultraviolet light removing said

photoprotective material from said at least a first surface of said glass plate under said first locations of said mask;

[g] f) exposing said first surface to a first amino acid, said first amino acid binding to regions of said at least a first surface from which said photoprotective material was removed, said first amino acid comprising said photoprotective group at a terminus thereof;

[h] g) placing a mask in contact with said glass plate at a second position;

[i] h) illuminating said mask with at least ultraviolet light, said ultraviolet light removing said photoprotective material from said at least a first surface of said glass plate under said first locations of said mask;

[j] i) exposing said at least a first surface to a second amino acid, said second amino acid binding to regions of said at least a first surface from which said photoprotective material was removed, said second amino acid comprising said photoprotective group at a terminus thereof;

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[k] j) placing a mask in contact with said glass plate at a third position;

[l] k) illuminating said mask with at least ultraviolet light, said ultraviolet light removing said photoprotective material from said at least a first surface of said glass plate under said first locations of said mask;

[m] l) exposing said at least a first surface to a third amino acid, said third amino acid binding to regions of said at least a first surface from which said photoprotective material was removed;

[n] m) placing a mask in contact with said glass plate at a fourth position;

[o] n) illuminating said mask with at least ultraviolet light, said ultraviolet light removing said photoprotective material from said at least a first surface of said glass plate under said first locations of said mask;

[p] o) exposing said at least a first surface to a fourth amino acid, said fourth amino acid binding to regions of said at least a first surface from which said photoprotective material was removed, said at least a first surface comprising at least first, second, third, and fourth amino acid sequences;

[q] p) exposing said at least a first surface to an antibody of interest, said antibody of interest binding more

strongly to at least one of said first, said second, said third, or said fourth amino acid sequences;

[r] q) exposing said at least a first surface to a receptor, said receptor recognizing said antibody of interest and binding at multiple locations thereof, said receptor comprising fluorescein;

[s] r) exposing said at least a first surface to light, said first surface fluorescing in at least a region where said more strongly bound amino acid sequence is located; and

[t] s) detecting and recording fluoresced light intensity as a function of location across said at least a first surface.

47. (Amended) The method as recited in claim 45 wherein said step of irradiating is a step of masking a light source with a mask, said mask comprising first transparent regions and second opaque regions, said transparent regions transmitting light from said source and said opaque regions blocking light from said source.

Please add the following new Claims 106-110:

--106. The method as recited in claim 6 wherein said first and second regions each have an area of less than about $1X10^6 \mu m^2$.

107. The method as recited in claim 6 wherein said steps are repeated to synthesize 10^4 or more different sequences on said substrate.

108. The method as recited in claim 6 wherein said steps are repeated to synthesize 10^5 or more different sequences on said substrate.

109. A method of screening polymer sequences for interaction with a receptor comprising the steps of:

exposing first selected regions of a surface to light to remove a protective group from said first selected regions;

washing at least second selected regions and said first selected regions with a material comprising a first monomer having a protective group;

exposing third selected regions to light, at least a portion of said third selected regions overlapping said first selected regions to remove a protective group from said third selected regions;

washing at least said second and third selected regions with a second monomer so as to from a plurality of polymer sequences in said substrate; and

exposing said polymers to said receptor and detecting a location on said substrate where said receptor binds.

110. The method as recited in claim 6 wherein said activator is electromagnetic radiation.--

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REMARKS

CONTENTS

I. General

On the face of the Office Action, the Examiner requires formal drawings, and the drafting division indicates various informalities with the drawings such as poor lettering and the like. Applicants filed formal drawings on August 30, 1990. These drawings meet the requirements of the drafting division.

Additionally, Applicants filed a petition on August 30, 1990 for allowing color drawings in the application. This petition has not been acted upon, and Applicants renew their request for favorable consideration thereof.

Further, Applicants filed a Request for Drawing Changes on August 30, 1990, in which Applicants requested permission to make minor editorial changes to the drawings. This request has

not been acted upon, and Applicants renew their request for favorable consideration thereof.

The Examiner's attention is drawn to the Supplemental Information Disclosure Statement filed on March 20, 1991 and which obviously crossed in the mail with the Office Action of the same date. Applicants also wish to acknowledge the effort that has been required on the part of the Examiner to examine the substantial volume of cited art.

The Examiner has noted that the application names joint inventors. The inventions claimed herein were all under an obligation of assignment to a common assignee at the time the inventions were made.

The Examiner states that the application incorporates by reference essential material from a foreign patent or a publication. Applicants are of course entitled to directly copy any such essential material into the specification by virtue of its incorporation by reference, and Applicants will enter any essential material by way of amendment. However, the Examiner has not indicated which material she deems to be essential, and clarification of this item is requested so as to avoid unnecessarily increasing the bulk of the application. Applicants do not believe that essential material was omitted from the specification; Applicants incorporated by reference various materials only in an abundance of caution.

Applicants have added new Claims 106-110 for the Examiner's consideration, which find extensive support in other claims and the specification. Minor editorial changes have also been noted and made in various claims.

II. Response to Restriction Requirement

The Examiner has imposed a restriction requirement on the application. By way of this amendment Applicants elect the Group II Claims 6, 7, 15, 26, 27, 36, 40, 41, 44-54, and 75. The non-elected claims have been cancelled without prejudice for later prosecution in a divisional or other related application. The dependencies of other claims have been modified.

The Examiner has noted that upon cancelling claims, the inventorship of the application must be amended if one or more inventors is no longer an inventor of the remaining subject matter. Applicants have made a good faith review of the remaining claims and believe that the named inventors each contributed

to the conception of the subject matter of at least one of the remaining claims.

III. Rejections Under 35 USC 112, Second Paragraph

Claims 6, 7, 15, 26, 27, 36, 40, and 41 have been rejected since they depend from claims which are not elected. Applicants have incorporated the limitations of Claim 1 into Claim 6. Applicants have incorporated the limitations of Claim 26 into Claims 19, 20, and 21 from which it depended. The dependencies of various dependent claims therefrom have also been appropriately amended.

Claim 6 has been rejected because Claim 1 does not clearly describe how polymers are formed on the substrate. The Examiner specifically states that the claim must describe what materials are needed to perform the steps, what is performed in the step, and what is achieved by the step. The Examiner cites Ex parte Erlich, 3 USPQ 2d 1011 (1986). It is respectfully reliance on Erlich is misplaced and, in fact, Erlich supports the patentability of the claims herein. Erlich states that a method claim must contain at least one method step; the claim involved in Erlich did "...not specifically recite any process steps." Ex parte Erlich, 3 USPQ2d 1011, 1017 (1986), emphasis added.

In the present case, Applicants clearly do recite process in Claim 6 which includes the steps of exposing a first region to an activator, exposing the first region to a first monomer, exposing a second region to an activator, exposing the second region to a second monomer, and screening the sequences for affinity with a receptor. Without question, this claim meets the test of Ex parte Erlich that a claim must "at least recite a positive active step(s)...." Id., emphasis added. Applicants may otherwise obtain claims commensurate with the scope of the disclosure and not obvious in view of the art. There is no authority for the proposition, and Applicants are not required to submit claims which "describe what materials are needed to perform the step, what is performed in the step, and what is achieved by the step." Applicants have met the statutory requirement to particularly point out and distinctly claim the invention.

Claims 15 and 36 are rejected because it is allegedly not clear how the marker is associated with the receptor. Again, the claim is perfectly clear; the marker may be covalently bound or otherwise associated with the receptor in any of the

myriad of ways well known to those of skill in the art, such as affinity type binding (e.g., with biotin). Such binding methods are well known to those of skill in the art and described in, e.g., Lowe et al. There is simply no justification for requiring that all of the details of particular embodiments of the invention be incorporated into a claim.

Claim 19 is rejected because it allegedly recites in the preamble first and second sequences comprising at least a first and a second monomer yet the body of the claim defines a "very different" first and second monomer. The language in the preamble to which the Examiner objects has been deleted.

The Examiner has suggested that Applicants add the word "each" at line 5 of Claim 19. The suggested amendment has been entered. The Examiner states at the bottom of page 8 of the Office Action that "it is not clear that the monomers bind such that the protective group is exposed and not the means by which the monomer binds." This objection is not understood and clarification is requested. The Examiner has suggested the addition of a comma between second region and deactivating in Claim 20. That comma has been entered.

The Examiner has requested that TFA be spelled out in Claim 44. The particular limitation referred to therein has been deleted and replaced with the term "a TBOC removal agent."

Claim 46 is objected to because it is not clear how the marker is "related" to the method of detection, or how it is used to detect. The claim calls for the use of the radioactive or fluorescent marker to detect which of the first or second sequence binds with the receptor. There is no ambiguity in the claim and would be no difficulty in ascertaining whether a particular process was infringed by the claim. As discussed in relation to other similar rejections of the above claims, Applicants are not required to specify particular aspects of preferred embodiments of the inventions in the claims.

The Examiner has rejected Claim 47 because it is not clear what purpose the mask serves. The claim has been amended to recite that the mask blocks light in the opaque regions and transmits light in the transparent regions.

Applicants have also noted and corrected several editorial items in the claims.

IV. Rejections Under 35 USC 103

Applicants have invented and claimed in the present application new methods for screening receptors which is of a pioneering nature. The methods provide order of magnitude increases in the speed of screening and the number of compounds which may be screened, providing a veritable revolution in the pharmaceutical industry, and biotechnology in general.

This pioneering technology is receiving wide-spread acclaim. Articles touting the method have appeared in Genetic Engineering News ("Affymax Teams Pioneer Rapid Drug Discovery Technologies"), Business Week ("This Tiny Chip Can Test 10,000 Chemicals at Once"), Chemical and Engineering News ("Technique Offers Parallel Synthesis of Thousands of Chemical Compounds"), The San Francisco Chronicle ("Breakthrough May Speed Drug Research") and other newspapers/journals. Of particular note is a review by three renowned biotechnology experts entitled "Light in Molecular Recognition" (Kaiser, Hunkapillar and Hood, Nature (1991) 350:656-657, a copy of which is enclosed). Kaiser et al. call the present technique "... a fresh way of tackling one of the fundamental problems of modern biology, namely molecular recognition." The presently claimed process has been the subject of a recent, peer-reviewed article in Science, which appeared on the cover of the February 14, 1991 issue.

Clearly, the method disclosed/claimed herein is much more than a mere combination of existing technologies, such as those of Lowe, Geysen, and Patchornik. With this is mind, the specific rejections are addressed below.

A. Rejections Over Lowe et al.

The Examiner has rejected Claims 6, 7, 15, and 75 under 35 USC 103 as allegedly being obvious over Lowe et al. For the reasons set forth below, reconsideration of the rejection and allowance of the claims are respectfully requested. It should be noted that several Lowe et al. references have been cited, and Applicants assume below that the rejection is over U.S. Patent No. 4,562,157. If this is not correct, the Examiner is requested to clarify the rejection and re-start the time for response.

An important goal of the invention claimed herein is the synthesis of diverse chemical sequences at known locations on a substrate, followed by the screening of these diverse sequences for interactions with, for example, an antibody or other receptor. Lowe et al. do not provide even a clue as to how this

goal would be achieved. Lowe et al. propose to attach a number of materials which have already been synthesized to a substrate. In, for example, Example 1 of Lowe et al., a process is described in which E. coli beta-galactosidase is attached to the surface of a substrate, after activation of 5 circular regions on the substrate. Beta-galactosidase is a large molecular weight, naturally occurring compound; thus, Lowe et al. do not show or suggest synthesis of diverse compounds. This problem of synthesizing large scale chemical diversity has plagued the art for many years and was not solved by Lowe et al. (who state that diverse materials are already available). Hence Lowe et al. presume that a variety of materials are available for use, and their interactions with other compounds are known. Although not entirely clear, Lowe et al. then propose to use these immobilized, pre-synthesized materials to test for the presence of a compound which is known to interact with the material (see, e.g., the specification and Claim 16), and did not propose the in situ synthesis of the ligand.

In contrast, applicants claim a method in Claim 6 wherein a first region of a substrate is exposed to an activator such as light, and the first region is exposed to a first monomer. A second region is then exposed to light, and exposed to a second monomer. Applicants have clarified the claims to recite that these steps are conducted so as to synthesize at least a first ligand and a second ligand on the substrate. See, e.g., Claim 6 which recites that the second region overlaps the first region. The diverse materials which have been synthesized according to the method are then screened by exposing the substrate to a receptor to evaluate their interaction with the receptor.

Lowe et al. do not show or suggest a variety of features of the invention recited in, e.g., Claim 6. Importantly, Lowe et al. do not show or suggest the synthesis of a ligand by way of sequential addition of a series of monomers to selected regions of a substrate in the manner claimed. No method for synthesizing diverse chemical sequences is shown or suggested. Moreover, Lowe et al. state that the fully synthesized materials are used merely to sense the presence of a compound; a method for screening ligands for interaction with a receptor is not shown or suggested in the manner recited in Claim 6.

The Examiner states that Lowe et al. disclose methods in which "two or more biochemical species can be selectively

bound to sensor surfaces." However, this is not what Applicants claim in clarified Claim 6. Instead, Applicants claim a particular synthesis of diverse chemical species on a substrate, a process not shown or suggested by Lowe et al.

The dependent claims recite the use of materials and methods which are not shown in Lowe et al. Claim 7, for example, recites an additional feature of the invention herein which is not shown or suggested in Lowe et al. Claim 7 recites that the receptor recited in Claim 6 is an antibody. The Examiner states that Lowe et al. teach that the ligand is a "species which is capable of participating in a binding reaction with a suitable partner, such as antigen-antibody." Lowe et al. disclose at column 9, line 47 et al. that the "ligand ...may be an antibody...." That is, Lowe et al. state that the material which is bound to the substrate may be an antibody. Lowe et al. do not show or suggest the subject matter of Claim 7, i.e., that a substrate with of a variety of surface synthesized polymers is exposed to an antibody for screening. Again, this additionally points out the fundamental difference between the disclosure of Lowe et al., and the invention claimed herein. Lowe et al. do not show or suggest the synthesis of chemical diversity which may be used for exploring the interaction of such diverse materials with, in the case of Claim 7, an antibody. Lowe et al. assume that these interactions are known in advance.

The Examiner states that the subject matter of the claims differs from the prior art, if at all in the specific recitation of the steps of the instant method. As shown above, the steps recited herein are not shown or suggested in Lowe et al., and the claimed method provides capabilities not shown therein. Hence, a prima facie case of obviousness is not presented. Moreover, as discussed in greater detail below, even if a prima facie case of obviousness had been presented, Applicants have demonstrated surprisingly beneficial results which would overcome the prima facie case.

B. Rejections Over Lowe et al. in view of Geysen

Claims 26, 27, 36, 40, and 41 stand rejected under 35 USC 103 as being obvious over Lowe et al. in view of Geysen. Again, several Lowe et al. and Geysen references are of record. Applicants assume below that the rejection is Lowe et al., U.S. Patent No. 4,562,157, in view of Geysen, U.S. Patent No. 4,833,092. If this is not correct, it is requested that

the Examiner clarify the rejection and restart the time for response.

Applicants have amended Claims 19, 20, and 21 to include the limitations of Claim 26 and Claim 26 has been cancelled. All of Claims 19, 20, and 21 recite a method of synthesizing chemical diversity on a substrate, and screening the synthesized compounds for interaction with a receptor.

As discussed extensively above, Lowe et al. do not show or suggest a method for synthesizing ligands on a substrate for screening with a receptor in the manner claimed, or for screening diverse ligands for interaction with a receptor. To the contrary, the work of Lowe et al. is based on the premise that diverse ligands are available for scrutiny, with known interactions with a receptor.

As explained below, the underlying concept in the Geysen reference appears to be a "short cut" for screening ligands for interaction with a receptor. The primary reason Geysen needs such a technique is because of his failure to devise a technique for efficiently synthesizing large numbers of ligands, a problem solved by the invention herein. The combination is addressed in detail below.

1. The Combination Fails to Present a Prima Facie Case of Obviousness

Applicants respectfully assert that the combination of Lowe et al. and Geysen fails to teach the invention as claimed. In, for example, Claim 19, a process is claimed in which a protective group is removed from a first region, a first monomer is applied thereto, etc. Lowe et al. describe the use of light to activate a photoactivatable compound. After this photoactivation, a material reacts with the activated location. Geysen describes synthesis of a number of compounds on support rods by standard techniques in which monomers are sequentially added to the support rods. Hence, Lowe et al. and Geysen still fail, in combination, to recite a method in which a group is removed from the substrate in the manner claimed. At best, the combination of the Lowe et al. and Geysen teachings would result in a process in which a region of a substrate is activated for binding with light without removal of the photoactivatable function. Hence, even if the references were combined (albeit improperly) in the manner suggested, the chain of monomers would be interspersed by photoactivatable groups resulting in a substrate of dubious value.

By virtue of Applicants claimed invention, in, for example, Claim 19, the photoactivatable group is removed. Neither Lowe et al. nor Geysen nor their combination teach removal of, e.g., the photoactivatable protective group in the manner claimed.

Assuming, arguendo, that the references did teach what the Examiner suggests, the Examiner has still failed to make a prima facie case of obviousness. In order to make a prima facie case, the Examiner must point to some motivation for one of skill in the art to make the combination as the Examiner has suggested. Such motivation is clearly lacking and, in fact, one of skill in the art would have been lead away from combining the references.

In particular, Lowe et al. teach a method for attaching a fully synthesized biochemical ligand to regions of a solid support, and which interact with the underlying support. The primary goal of Lowe et al.'s process is to generate field effect transistors on the surface of the substrate. Lowe et al. do not show or suggest that a "monomer" should be added to the biochemical ligand, and they do not show how such addition could be accomplished. To the contrary, adding a second material to a region where a first material had been attached would result in inoperative or less useful devices since an important goal of Lowe et al. apparently is to have each FET test for the presence of an anticipated receptor. The reason light directed attachment is used in Lowe et al. is specifically for the purpose of assuring that "individual" biochemical ligands are attached within any given region. One of skill in the art would not be motivated to use the teachings of Lowe et al. to attach multiple monomers within a single region to synthesize a ligand in the manner claimed.

Conversely, one of skill in the art would not be motivated upon reviewing the disclosure of Geysen to combine the teachings therein with those of Lowe et al. The disclosure of Geysen deals in large part with a multistep strategy for analyzing the interaction of a small polymer with a receptor and, based on that interaction, making a group of larger related polymers for further testing. The need for such complicated, multistep techniques arises from a fundamental problem in the field that essentially remained unaddressed until the invention herein: it was very difficult and time consuming to synthesize large numbers of diverse polymer sequences for biological screening. Based on the teachings of Geysen, one of skill in the art would certainly not turn to a reference which provided for

the use of fully synthesized materials whose interactions with a receptor were already known (i.e., Lowe et al.).

From the above it is seen that a prima facie case of obviousness is not presented for Claims 26, 27, 36, 40, and 41.

The Examiner states that it would be [would have been] obvious to combine the references because "both Lowe et al. and Geysen teach methods in which more than one ligand is immobilized on a solid support." As discussed above, there is in fact no explicit suggestion or suggestion as a whole to combine the references in the manner suggested by the Examiner. In fact, when viewed as a whole, it is seen that one of skill in the art would be lead away from making the suggested combination. Lowe et al. deal with the problem of screening for the presence of selected receptors with ligands with known interaction with the receptor; Lowe et al. do not suggest (or enable) the use of their technology for synthesizing and screening large numbers of ligands to determine which of the ligands interacts with a receptor. By contrast, Geysen is attempting to overcome the serious limitations with the standard synthesis technique disclosed therein by developing a "short-cut" to determining which of a few, short chain ligands interact with a receptor and extrapolating these results to longer ligands. Clearly there is no suggestion to use the technique described and claimed herein in which vast numbers of ligands are quickly and easily synthesized for screening, rendering the technique of Geysen of limited or no importance.

Moreover, other features recited in the claims are not found anywhere in the references. For example, in Claim 40 Applicants recite a method in which a second, labelled receptor is bound to multiple sites on the first receptor. This provides a fluorescent or other signal that is magnified several times over that of a the first receptor. These features are not shown or suggested in the cited references.

2. Even if, Arguendo, a Prima Facie Case was Presented, the Claims are Patentable

Even if, arguendo, a prima facie case of obviousness has been presented, Applicants have demonstrated substantial benefits of the presently claimed process which demonstrate the non-obviousness of the invention. The disclosure of Geysen does not specifically address the number of diverse sequences that are synthesized. A related paper by the same group (Geysen et al.,

"Strategies for Epitope Analysis Using Peptide Synthesis," J. of Immunological Methods, (1987) 102:259-274) discusses an array of 8x12 (96) pins. Geysen et al. state therein that it has taken this group 3 years to synthesize/screen 200,000 peptides! This number of peptides is readily synthesized/screened on only one or a few "chips" using the techniques herein. For example, using synthesis regions as large as 500x500 microns (e.g., Example I), the claimed technique provides approximately 200,000 amino acid sequences on just 10 "chips" having a radius of about 4 cm. Therefore, it is now possible to synthesize orders of magnitude more polymer sequences in orders of magnitude less time using the techniques disclosed herein as compared to Geysen. Using the techniques of Geysen, it would become almost a life's work to synthesize the large number of ligands made available using the techniques claimed herein. Therefore, even if a prima facie case of obviousness was presented, the benefits of the present invention would be sufficient to overcome the prima facie case.

c. Rejections Over Lowe et al. in view of Geysen and further in view of Patchornik et al.

The Examiner has rejected Claims 44-54 under 35 USC 103 as being unpatentable over Lowe et al. in view of Geysen and further in view of Patchornik et al. This rejection is also respectfully traversed. Patchornik et al. merely describes bulk reaction of two materials after exposure to light.

Claims 44-54 contain many of the limitations discussed above and it is asserted that the combination of Geysen and Lowe et al. is inappropriate for the reasons set forth above. Moreover, Claims 44-54 contain many limitations not found in any of the references. For example, Claim 44 contains limitations directed to the use of a reactor whereby fluids may be easily flowed through a cavity for faster synthesis; wherein UV light is utilized; wherein a receptor is utilized which binds to the antibody at multiple locations; and wherein various locations of the substrate are sequentially scanned and recorded for fluorescence intensity. None of these features are shown or suggested in the cited references in the manner claimed and, therefore, a prima facie case of obviousness is not presented.

Further, it is asserted that the combination of Patchornik et al. with that of Geysen and Lowe et al. is also improper. As discussed above, there must be some suggestion

either explicitly or when viewed as a whole to combine the references in the manner suggested. This motivation is lacking. In particular, Lowe et al. do not disclose a photoremovable group such as NVOC/NBOC. Instead, Lowe et al. discuss a photoactivatable group which is not removed upon exposure to light. Of course, removal of the photoactivatable group of Lowe et al. through use of the photoremovable group of Patchornik et al. would be contrary to the disclosure of Lowe et al. because the underlying group is not reactive, and nothing would be bound to the substrate if this group was removed. Based on this disclosure, one of skill in the art would not be motivated to look for groups that are removed upon exposure to light. Clearly, the combination of a photoremovable group with the disclosure of Lowe et al. would not be suggested to one of skill in the art.

V. Newly Located References

Applicants have recently located additional references listed in the enclosed Third Supplemental Information Disclosure Statement for the Examiner's consideration. Applicants appreciate the Examiner's attention to these references.

SUMMARY

For the reasons set forth above, it is respectfully asserted that the claims are in condition for allowance and allowance thereof is respectfully requested. If the Examiner believes a telephone conversation or in-person interview would facilitate prosecution of the application, the Examiner is invited to contact the undersigned attorney at (415) 326-2400.

Respectfully submitted,
TOWNSEND and TOWNSEND

Date: 8/20/91

By: Vern Norviel
Vern Norviel
Reg. No. 32,483

Enclosures:

1. Copy of Nature article by Kaiser et al.
2. Third Supplemental Information Disclosure Statement

VN:dc
WP50/11509/A-1-1.P22

EXHIBIT K

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT L

EXHIBIT REDACTED IN ITS ENTIRETY

EXHIBIT M

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Assistant Commissioner for Patents
Washington, D.C. 20231

On _____

TOWNSEND and TOWNSEND and CREW LLP

By: _____

PATENT
Attorney Docket No.: 18547-000181US
Client Reference No.: 1000.1b3

6-30-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Stephen P.A. Fodor
(as previously amended)

Application No.: 08/456,598

Filed: June 1, 1995

For: SIGNAL DETECTION METHODS AND APPARATUS

Examiner: J. Riley

Art Unit: 1655

AMENDMENT

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00 MAY 15 PM 5:21
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Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed February 1, 2000, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend the claims as follows.

31 154. (Twice amended) An apparatus for detecting labeled [nucleic acids] ~~receptors~~ receptors; comprising:

(a) a substrate having a surface comprising at least 10 different nucleic acids at known locations on the surface of the substrate, each of the known locations having an area of [1 cm or less], some of the nucleic acids being bound to labeled [nucleic acids] receptors;

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(b) an excitation light source;

(c) a detector adapted to receive a signal from said bound labeled [nucleic acid] receptors on said surface;

(d) a translator adapted to move said substrate relative to said detector; and

(e) a data collection system adapted to receive input from said detector.

Claims 155-159: Please delete "claim 154" and replace with –claim 160--.

Please add the following new claim:

160. The apparatus of claim 154, wherein the labelled receptors are labelled nucleic acids.

REMARKS:

Claim 154 is amended to recite that the target molecules analyzed by the array are the receptors (e.g., nucleic acids or proteins) in conformity with the teaching of the specification that nucleic acid arrays are also useful for analyzing a variety of receptors (see, e.g., paragraph bridging pp. 15-16). Dependent claim 160 is now directed to nucleic acids.

The sole outstanding rejection of the claims is the obviousness rejection over Southern, WO 89/10977 in view of Van der Voot. The office action acknowledges that the present application derives priority from USSN 07/362,901, filed June 7, 1989, which is before publication date of the Southern reference. However, the Examiner says that the '901 priority application does not provide 35 USC 112, first paragraph written description of all paragraphs. Applicants assume for purposes of this discussion only that the Examiner is correct. Neverthless, Applicants submit that insofar as Southern is asserted to disclose material that renders the present claims obvious, then the '901 priority application discloses at least the same subject matter, and that such is sufficient to antedate Southern.

Applicants note that the underlying legal issue was discussed in a telephone conference between the Examiner, Supervising Examiner Jones, Biotechnology Specialist Richard Schwartz and appliants' attorneys. In brief, agreement was reached that when a

reference is alleged to disclose the basic concept of a claimed invention, then the reference can be antedated under 37 CFR 131 by a declaration showing completion of as much of the invention is disclosed by the reference (see MPEP 715.02 and In re Stempel, 113 USPQ 77 (CCPA 1957)). It was further agreed that a primary reference discloses the basic concept of the invention when such details as the primary reference omits are well known in the art prior to the date of the primary reference (MPEP 715.02). Further, although a 131 declaration usually shows prior invention based on notebook pages and the like, it was agreed that prior invention could also be shown from a constructive reduction to practice in a US patent application. This practice is discussed in the concurring opinion of Judge Baldwin in In re Scheiber, 199 USPQ 722 (CCPA 1978).

Here, the Examiner is effectively alleging that Southern discloses the basic concept of the present claims. This is because the details that Southern omits are said by the Examiner to be known in the art through a secondary reference published well before Southern. Accordingly, Applicants can antedate Southern by a 131 declaration showing prior possession of so much of their claimed invention as Southern discloses.

Applicants attach a 131 declaration that shows that the present inventors had constructively reduced to practice at least as much as Southern discloses. In fact, Southern provides only very limited discussion pertinent to an apparatus for optical detection of labelled receptors bound to a nucleic acid array, as claimed. As discussed previously in prosecution, all of Southern's examples use radiolabels for analysis of hybridization to arrays. The only section of Southern relevant to optical detection is at p. 14, in which he says "obviously some direct detection system would be better. Fluorescent probes are envisaged; given the high concentration of the target oligonucleotides, the low sensitivity of fluorescence may not be a problem." .Thus, at most, Southern discusses the possibility of using a fluorescent label to analyze polynucleotide targets bound to nucleic arrays.

The attached declaration shows that the present inventors had completed invention of at least this subject matter in the '901 priority document. The inventors identify the pertinent sections of the application in paragraph (4) of the declaration. Specifically, the '901 application discloses arrays of nucleic acids, use of same to bind fluorescently labelled receptors, including DNA, and optical detection of the same. Accordingly, the present

inventors were in possession of at least as much as Southern. Therefore, Southern is antedated as a reference and the rejection should be withdrawn.

The 131 declaration is being filed simply to expedite prosecution and should not be construed as an acquiescence in the merits of any ground of rejection.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

Joe Liebeschuetz
Reg. No. 37,505

May 15, 2000

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EXHIBIT N

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

6/C
B. Webb
5/15/00

In re Patent Application of

FODOR et al.

Appln. No. 09/362,089 Group Art Unit: 1643

Filed: July 28, 1999 Examiner: Not known

FOR: A METHOD OF DETECTING NUCLEIC ACIDS

* * *

May 2, 2000

THIRD PRELIMINARY AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Please enter the following amendments before substantive examination of the present application.

IN THE CLAIMS:

Kindly add the following new claims.

sub D2 C1

--58. A method of analyzing a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents and an encoding system, whereby one or more of the substrates bind to the target via the reagent; and

(b) identifying the reagent on the substrate bound to the target using the encoding system.

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21 ~~59~~. The method of claim 20 ~~58~~, wherein the reagent is a probe.

22 ~~60~~. The method of claim 21 ~~59~~, wherein the probe is an oligonucleotide.

23 ~~61~~. The method of claim 20 ~~58~~, wherein the target molecule is a polymer.

C1 Cont

24 ~~62~~. The method of claim 23 ~~61~~, wherein the target molecule is a polynucleotide.

25 ~~63~~. The method of claim 23 ~~61~~, wherein the target molecule is a polypeptide.

26 ~~64~~. The method of claim 20 ~~58~~, wherein the target molecule is a nucleic acid.

27 ~~65~~. The method of claim 20 ~~58~~, wherein the substrates are impregnated with a fluorescent molecule.

Sub E4

28 ~~66~~. The method of claim 20a ~~58~~, wherein the encoding system is a magnetic system, shape encoding system, color encoding system, or a combination thereof.

29 67. The method of claim ~~58~~ 20, wherein the substrates are beads.

30 68. The method of claim ~~58~~ 20, wherein the substrates are fibers.

31 69. The method of claim ~~58~~ 20, wherein the substrates comprise glass.

Cl cont 32 70. The method of claim ~~69~~ 31, wherein the glass is a microscope slide.

33 71. The method of claim ~~58~~ 20, wherein the substrates have a three dimensional contour.

34 72. The method of claim ~~58~~ 20, wherein the reagent is an oligomer.

35 73. The method of claim ~~72~~ 34, wherein the oligomer is a nucleic acid.

36 74. The method of claim 72 34, wherein the oligomer comprises nucleotides.

37 75. The method of claim ~~72~~ 34, wherein the oligomer is a peptide.

Concl'd 38/76. The method of claim ~~58~~ 20, wherein the reagent is an oligonucleotide.--

REMARKS

Claims 26-76 are pending.

The amendments to the claims find support throughout the original disclosure. In particular, the new claims added here are similar to the claims added in the Second Preliminary Amendment of January 6, 2000. Comparing claims 39 and 58, the difference between them is that claim 58 does not require separating bound and unbound substrates. See the chart in the Second Preliminary Amendment for citation of support in the specification for these claims.

The new claims are directed to an invention disclosed in the specification, but not originally claimed. No new matter has been added by these amendments.

An early and favorable examination on the merits is earnestly solicited.

Respectfully submitted,

Cushman Darby & Cushman
Intellectual Property Group of
PILLSBURY MADISON & SUTRO, L.L.P.

By [signature] 43,180
for Paul N. Kokulis
Reg. No. 16,773
Telephone: (202) 861-3503
Facsimile: (202) 822-0944

EXHIBIT O

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re Patent Application of

FODOR et al.

Appln. No. 09/362,089

Filed: July 28, 1999

Group Art Unit: 1655

Examiner: S. Zitomer

FOR: ANALYSIS OF TARGET MOLECULES USING AN ENCODING SYSTEM (as amended)

13/B
B. Webb
3/8/01

* * *

February 28, 2001

AMENDMENT UNDER 37 CFR § 1.111

Hon. Commissioner for Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action mailed August 28, 2000 (Paper No. 9), entry and consideration of the following amendment and remarks are requested.

IN THE TITLE:

Kindly replace the title wherever it appears in the application (e.g., cover sheet, page 1, and page 142 of the substitute specification) with --ANALYSIS OF TARGET MOLECULES USING AN ENCODING SYSTEM--.

IN THE CLAIMS:

Kindly amend the claims as follows.

Sub F1

39. (Amended) A method of analyzing a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents [and an encoding system],

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whereby one or more of the substrates bind to the target via the reagent, and an individual bound substrate thereby bears a tag of an encoding system;

(b) separating the substrates that bind the target from the substrates that do not bind the target; and

(c) identifying the reagent on a separated substrate [using the encoding system] by reading the tag on the separated substrate.

58. (Amended) A method of analyzing a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents [and an encoding system], whereby one or more of the substrates bind to the target via the reagent, and an individual bound substrate thereby bears a tag of an encoding system; and

(b) identifying the reagent on the substrate bound to the target [using the encoding system] by reading the tag on the individual bound substrate.

Kindly cancel claims 26-38 without prejudice and add the following claims:

–77. A method of analyzing a target nucleic acid in a sample, comprising:

(a) contacting the target with a collection of beads, wherein different beads bear different probe nucleic acids, whereby one or more of the beads bind to the target via hybridization between the probe and the target,

and an individual bound bead thereby bears a tag of an encoding system; and

(b) identifying the different probes on the one or more beads which are bound to the target by reading the tag on the individual bound bead.

78. A method of analyzing a target nucleic acid in a sample according to the method of claim 77 and further comprising sorting the one or more beads that bind to the target from beads that do not bind to the target.

41~~78~~. The method of claim ~~78~~ 40, wherein the beads are sorted with a cell sorting device.

42~~80~~. The method of claim ~~77~~ 39, wherein at least one of the different probes is an oligonucleotide.

43~~81~~. The method of claim ~~77~~ 39, wherein at least one of the different probes is a polynucleotide.

44~~82~~. The method of claim ~~77~~ 39, wherein the bead is tagged with a fluorescent tag of a color encoding system.

45~~83~~. The method of claim ~~77~~ 39, wherein the target nucleic acid has a label and hybridization results in the individual bound bead to be tagged with the label.

46 84. The method of claim 45 83, wherein the label is a green or red fluorescent label.

47 85. The method of claim 45 83, wherein the label is selected from the group consisting of radioisotopes, chemiluminescent or bioluminescent compounds, chromogens, heavy metal atoms, electron spin labels, magnetic labels, enzyme-linked labels, and labeled binding proteins.

D3 cont'd

48 86. The method of claim 39 77, wherein the encoding system is a magnetic system, shape encoding system, color encoding system, or a combination thereof.

49 87. The method of claim 39 77, wherein the collection of beads has at least 10^2 different probes.

50 88. The method of claim 39 77, wherein the collection of beads has at least 10^3 different probes.

51 89. The method of claim 39 77, wherein the collection of beads has at least 10^4 different probes.

52 90. The method of claim 39 77, wherein the collection of beads has at least 10^5 different probes.

D

D3 Cancel ~~53-91.~~ The method of claim ~~77~~ 39, wherein the collection of beads has at least 10^6 different probes.–

REMARKS

Reconsideration and allowance are respectfully requested.

Applicants acknowledge with appreciation the Examiner's courtesy in granting the interview of November 9, 2000.

Claims 39-91 are pending. Applicants affirm election of Group III (claims 39-76) in response to the Examiner's restriction requirement. Non-elected claims 26-38 were withdrawn from consideration by the Examiner. Applicants have canceled the non-elected claims without prejudice, and filed divisional applications directed to that subject matter.

It was indicated on page 3 of the Action that the substitute specification would not be entered because it is incomplete. In response, Applicants respectfully request that the Examiner review the original and substitute specifications, and ensure that they were not switched during processing of this application. If another copy of the substitute specification is required, Applicants would provide it to the Examiner.

The claim amendments are supported by the original disclosure and, thus, do not add new matter. If the Examiner should disagree, she is respectfully requested to point out the challenged limitation in the next Office Action so support can be cited in response. For example, claims 39 and 58 are supported by the disclosure from page 36, last paragraph, to page 37, second paragraph, of the substitute specification as applied to analysis of target molecules (e.g., sequence information, fingerprint information, or mapping information). New claims 77-91 were added to more

particularly describe the bead embodiment of the invention. Page 12, last paragraph, of the substitute specification describes different minimum numbers of probes on the substrates. Page 41, third paragraph; page 48, second paragraph; page 56, third paragraph; and pages 84-87 of the substitute specification show particular examples of tags and labels that can encode the bound substrate.

35 U.S.C. § 112 – Written Description

Claims 39-76 were rejected under Section 112, first paragraph, as allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse because the guidance that the Examiner alleges would be required but is absent from this specification would have been known to persons skilled in the art at the time this application was filed. A patent need not teach, and preferably omits, what is well known in the art. *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

To clarify the use of the encoding system and its relationship to the substrate bound to target, the term "label" or "tag" has been used in the claims to indicate the entity that is to be read on the bound substrate and which identifies the reagent. Tag is used more generally as part of the encoding system, and label is used as a tag which is on the substrate through binding to the target (i.e., the target is labeled and the label is attached to the substrate through the target).

Applicants' substitute specification states on page 37, second paragraph, "An encoding system may include a magnetic system, a shape encoding system, a color

encoding system, or a combination of any of these, or any other encoding system." It was alleged on page 4 of the Action that a person skilled in the art "would not have known *a priori* which 'encoding system' or combination of 'encoding systems' would be workable with the claimed invention absent some guidance in the specification." But Applicants submit that this is an incorrect characterization of their disclosure and the general knowledge available to persons skilled in the art.

As quoted above, Applicants' specification teaches various encoding systems suitable for use in the claimed invention. The tags and labels suitable for use in an encoding system are described on page 41, third paragraph; page 48, second paragraph; page 56, third paragraph; and pages 84-87 of the substitute specification. A magnetic encoding system, for example, could use magnetic probes as taught on page 41, third paragraph, of the substitute specification or transponders as disclosed in the U.S. patents as cited by Mandecki on col. 5, lines 1 and 5, of U.S. Patent No. 5,641,634. Combining such systems would be routine given the skill in the art. Thus, such systems were known although they were not previously used as in the claimed invention. This shows that the chemical structure of the "encoding system" is taught in this specification and that person skilled in the art would know how to make and use such tags and labels as part of the encoding system.

When the description of the "encoding system" (pages 36-37) is read in light of the rest of Applicants' specification, especially the description of "coding" applications and the use of nucleotide sequences for encoding on pages 95-99 of the substitute specification, a person of skill in the art would recognize that the pending claims are supported by a broad disclosure of Applicants' invention.

It was further alleged on page 4 of the Action that it is not taught "whether 'the encoding system' is part of the substrate which bears the reagents or is a separate entity." Applicants submit that an explicit teaching in this specification is not required because the prophetic example on pages 36-37 of the substitute specification (i.e., reading the encoding system to determine the specificity of the reagent on the bead) implies that the tag of the encoding system is borne on the substrate at least after that substrate is bound to the target because sorting bound from unbound does not separate the tag from the bound substrate. Only if the bound substrate itself bears the tag could the encoding system be "read off" after sorting.

Another statement on page 4 appears to ask whether the encoding system and the substrate are "separate entities." This is answered by the implied teaching on page 37 of the substitute specification that it is the substrate bound to target which is encoded ("beads which do bind might be encoded"). Thus, depending on whether a tag of the encoding system is on the substrate or on the target before binding, the encoding system may or may not be attached directly to the substrate at the initiation of the process. For example, if the target was initially tagged then the substrate could become indirectly tagged after binding. But the tag may also be directly attached to the substrate and, thus, they would not be separate entities. In either situation, the encoding system would be borne by the substrate after binding to the target. Alternatively, Applicants describe intercalating dyes (e.g., ethidium bromide) that become part of the bound substrate by intercalating into the double helix of hybridized target and reagent on page 84, third paragraph, of the substitute specification. Such labels would be separate from the target, the substrate, and the reagent before binding and be read off the substrate after binding.

Applicants request withdrawal of the claim rejection made under Section 112, first paragraph, because this specification conveys to a person skilled in the art with reasonable clarity that Applicants were in possession of an encoding system that can be used in claimed invention. Their disclosure would also teach a skilled person, who possesses general knowledge available in the art, how to make and use tags of the encoding system suitable for the claimed invention.

Upon withdrawal of the rejection under Section 112, first paragraph, the latest priority date of this application would be December 20, 1990 because this application would be entitled to an earlier effective filing date under Section 120.

35 U.S.C. § 112 - Definiteness

Claims 39-76 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The syntax of claims 39 and 58 has been clarified in response to the objection raised on page 4 of the Action. In particular, the claims as amended make clear that (1) the reagent and tag are different entities, (2) an individual bound substrate bears a tag of an encoding system, and (3) the tag of the encoding system is on the bound substrate at least after binding.

Applicants request withdrawal of the claim rejection made under Section 112, second paragraph, because the pending claims are clear and definite.

35 U.S.C. § 102 - Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 39-40, 42, 44, 47-48, 52, 56, 58-59, 61, 63, 66-67, 71 and 75 were rejected under Section 102(b) as allegedly anticipated by Mochida et al. (UK Patent Appln. No. 2,129,551). Applicants traverse.

Mochida teaches a tag on an assay vessel or a reaction container. The tag can contain information about various characteristics of the assay. It also appears that the reagent may be on the assay vessel *per se* such that the vessel acts as a reaction container. When antibody reagents are on beads, however, the reference fails to disclose that the tag is on the bead. In such a situation, the assay vessel is tagged but the bound bead does not bear the tag.

Furthermore, even in those cases in which the substrate is tagged (i.e., the tag on the reaction container), Mochida does not separate the substrates that bind target via the reagent (i.e., bound substrates) from those that do not bind target (i.e., unbound substrates). Thus, claim 39 is not anticipated by the reference because the separation step is a required limitation of the method.

Assay information provided by the tag is apparently not directed to the identity of the reagent. Instead, Mochida discloses that the information given are characteristics such as the identity of the standard specimen, its lot number, and the calibration curve. Claims 39 and 58 are not anticipated by the reference because the reagent

cannot be identified by reading the tag on the bound or separated substrate. This failure is not surprising because identification of the reagent on the substrate is not Mochida's objective. Mochida apparently is only using one type of reagent for each assay instead of different substrates bearing different reagents. Thus, claims 39 and 58 are also not anticipated by the reference because providing different substrates bearing different reagents is a required limitation of both methods.

Mochida does not anticipate the claimed invention because all limitations of independent claim 39 or 58 are not found in the reference. Moreover, those claims depending from the independent claims are also not anticipated by the reference because the limitations of claims 39 or 58 are incorporated in the dependent claims. See *In re McCarn* 101 USPQ 411, 413 (C.C.P.A. 1954).

Claims 39-45, 48, 50, 52-64, 67, 69 and 71-76 were rejected under Section 102(b) as allegedly anticipated by Mandecki (US Patent No. 5,641,634). Applicants traverse because the reference is not prior art. The reference date of Mandecki is June 24, 1997 under Section 102(b) and November 30, 1995 under Section 102(e), but this application is entitled to a priority date of at least December 6, 1990 by a series of continuation and divisional application. Thus, Mandecki does not anticipate the claimed invention.

Claims 39-45, 47-50, 52-64, 66-69 and 71-76 were rejected under Section 102(b) as allegedly anticipated by Nova et al. (US Patent No. 5,751,629). Applicants traverse because the reference is not prior art. The earliest reference date that Nova et al. would appear to be entitled to under Section 102(e) is April 25, 1995, but this application is entitled to a priority date of at least December 6, 1990 by a series of

continuation and divisional application. Thus, Nova et al. does not anticipate the claimed invention.

For the above reasons, it is submitted that the claim rejections made under Section 102 should be withdrawn.

35 U.S.C. § 103 – Nonobviousness

To establish a case of *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a *prima facie* case of obviousness without some evidence that supplies the impetus to combine those teachings in the manner proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may

be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however, broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id.* Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 46, 51, 65 and 70 were rejected under Section 103(a) as allegedly unpatentable over Mochida et al. as applied to claims 39-40, 42, 44, 47-48, 52, 56, 58-59, 61, 63, 66-67, 71 and 75 above and further in view of Southern (US Patent No. 5,700,637). Applicants traverse.

The failure of Mochida to disclose the claimed invention is not remedied by the attempt to modify that disclosure with Southern. Among those failures are the lack of a separation step, the inability to identify the reagent by reading the tag on the bound or separated substrate, and the absence of different substrates bearing different reagents.

Apparently, Southern was cited for other reasons having to do with impregnating substrates with a fluorescent molecule and using glass microscope slides as substrates. But a review of Southern does not show that it addresses Mochida's deficiencies or even attempts to address those types of problems.

Finally, Applicants submit that there would be no motivation to combine the references or a reasonable expectation of success because of the disparate objectives and technologies of Mochida and Southern.

For the above reasons, it is submitted that the claim rejection made under Section 103(a) should be withdrawn because all limitations of independent claim 39 or 58 are not found or suggested in the cited references. Moreover, claims depending from those independent claims are also not made obvious by the references because the limitations of claims 39 or 58 are incorporated in the dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Having fully responded to the objections and rejections in the pending Office Action (Paper No. 9), Applicants submit that the pending claims are in condition for allowance and earnestly solicit an early Notice of same. If further information is needed, the Examiner is invited to contact the undersigned.

Respectfully submitted,

Intellectual Property Group of
PILLSBURY WINTHROP L.L.P.

By _____ 43,180
for Paul N. Kokulis
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EXHIBIT P

Interview Summary

Application No.	Applicant(s)	
09/362,089	FODOR et al.	
Examiner	Group Art Unit	
S. ZITOMER	1655	

All participants (applicant, applicant's representative, PTO personnel):

(1) *S.Zitomer* (3) _____

(2) *Paul Kokulis For Applicant* (4) _____

Date of Interview *Sep 20, 2001*

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy is ~~given to~~ mailed 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No. If yes, brief description:

Claim(s) discussed: *39, 47, 58, and 77*

Identification of prior art discussed:

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments:

The 112, first paragraph, rejection for lack of written description was dicussed and examiner agreed that applicant's arguments overcame the rejection. Changes to the claims to clarify distinction between the encoding system and the reagent as a binding reagent were discussed and accepted. Examiner agreed that claim 47 should be restored to its original scope.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i)☐ It is not necessary for applicant to provide a separate record of the substance of the interview (if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached

S. Zitomer
PRIMARY EXAMINER

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

EXHIBIT Q

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

FODOR ET AL

Serial No. 09/362,089

Filed: July 28, 1999

For: ANALYSIS OF TARGET MOLECULES USING AN ENCODING SYSTEM

Group Art Unit: 1655

Examiner: Zitomer

September 25, 2001
Via Facsimile

SUPPLEMENTAL AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Supplementing the applicants' amendment of September 17, 2001, please amend the above application as follows:

IN THE CLAIMS

Please enter the following amended claims:

1 ~~39~~. (Thrice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different binding reagents and a binding reagent encoding system, whereby the target molecule binds to one or more of the substrates via the reagent;

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(b) separating the substrates that bind the target molecule from the substrates that do not bind the target molecule; and

(c) identifying the reagent on a separated substrate by reading the binding reagent encoding system on the separated substrate and thereby identifying said bound target molecule.

72

9 ~~87~~. (Twice Amended) The method of claim ~~39~~ 1, wherein the encoding system is a magnetic system, shape encoding system, color endocing system, or a combination thereof.

73

~~88~~ 20. (Thrice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molcule with a collection of substrates, wherein different substrates bear different binding reagents and a reagent encoding system, whereby one or more of the substrates bind to the target molecule via the binding reagent; and

(b) identifying the binding reagent on the substrate bound to the target by reading the reagent encoding system on the individual bound substrate and thereby identifying said target molecule.

74

28 ~~85~~. (Twice Amended) The method of claim ~~88~~ 20, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

39 77. (Twice Amended) A method of identifying a target nucleic acid in a sample, comprising:

(a) contacting the target nucleic acid with a collection of beads, wherein different beads bear different probe nucleic acids and a probe encoding system, whereby one or more of the beads bind to the target nucleic acid via hybridization between the probe nucleic acid and the target nucleic acid; and

(b) identifying the different probes on the one or more beads which are bound to the target nucleic acid by reading the encoding system on the individual target bound bead and thereby identifying said target nucleic acid.

40 78. (Twice Amended) A method of identifying a target nucleic acid in a sample according to the method of claim 77 and further comprising sorting the one or more beads that bind to the target nucleic acid from beads that do not bind to the target nucleic acid.

46 86. (Twice Amended) The method of claim 77, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

REMARKS

The applicants appreciate the courtesy and helpfulness extended by Examiner Zitomer to the undersigned at the interview on September 20th.

The claims have been amended as discussed with the Examiner in order to improve the form of the claims and the definition of the applicants' invention. The changes made in the claims are thought to be consistent with those discussed with the Examiner and allowance of the application is believed to be in order for the reasons advanced in the applicants' earlier response of September 17, 2001.

Claims 47, 66 and 86 have been returned to their previous form as it is understood that the Examiner agrees with the applicants that the various encoding systems recited in these claims find full support in the applicants' disclosure. See, for example, page 37, 1st full ¶ of the applicants' substitute specification.

The changes in the claims are highlighted in the attached Appendix.

Favorable action is requested.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By_____
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1600 Tysons Boulevard
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Phone: (703) 905-2118

APPENDIX

Version with Markings to Show Changes Made

IN THE CLAIMS

The claims have been amended as follows:

39. (Thrice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different binding reagents and [an] a binding reagent encoding system, whereby the target molecule binds to one or more of the substrates [bind to the target] via the reagent;

(b) separating the substrates that bind the target molecule from the substrates that do not bind the target molecule; and

(c) identifying the reagent on a separated substrate by reading the binding reagent encoding system on the separated substrate and thereby identifying said bound target molecule.

47. (Twice Amended) The method of claim 39, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

58. (Thrice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different binding reagents and [an] a reagent encoding system, whereby one or more of the substrates bind to the target molecule via the binding reagent; and

(b) identifying the binding reagent on the substrate bound to the target by reading the reagent encoding system on the individual bound substrate and thereby identifying said target molecule.

66. (Twice Amended) The method of claim 58, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

77. (Twice Amended) A method of identifying a target nucleic acid in a sample, comprising:

(a) contacting the target nucleic acid with a collection of beads, wherein different beads bear different probe nucleic acids and [an] a probe encoding system, whereby one or more of the beads bind to the target nucleic acid via hybridization between the probe nucleic acid and the target nucleic acid; and

(b) identifying the different probes on the one or more beads which are bound to the target nucleic acid by reading the encoding system on the individual target bound bead and thereby identifying said target nucleic acid [molecule].

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78. (Twice Amended) A method of identifying a target nucleic acid in a sample according to the method of claim 77 and further comprising sorting the one or more beads that bind to the target nucleic acid from beads that do not bind to the target nucleic acid.

86. (Twice Amended) The method of claim 77, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

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